REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 112, are respectfully requested in light of the following remarks.

STATUS OF CLAIMS AND AMENDMENTS

Claims 1, 9-11, 13, 14, 16, 17, 21, 24, 25, 27-29, 43-51 and 61-66 are now in this application. Claims 33, 35-42 and 52-60 have been cancelled by the foregoing amendment, without prejudice or disclaimer. Claims 61-66 have been added.

Claims 1, 24, 25 and 27-29 have been amended to limit (i) to aspartylglucosaminidase (AGA); this amendment imposes this limitation on all of Claims 1, 9-11, 13, 14, 16, 17, 21, 24, 25, 27-29 and 43-51. Claims 33 and 35-42 as well as their dependent claims, Claims 52-60, have therefore been cancelled as redundant. The claims have been limited in this manner in order to expedite and simplify prosecution of this application.

Claims 1, 24, 25 and 27-29 have also been amended so that they require aspartylglucosaminidase (AGA) and do not require but rather specify as optional at least one "activator", now referred to for further clarity in the claims as at least one compound which stimulates the activity of aspartylglucosaminidase (AGA). These amendments are thus imposed on all of Claims 1, 9-11, 13, 14, 16, 17, 21, 24, 25, 27-29 and 43-51, although Claims 43-51 are in fact limited to specific "activators". New Claims 61-66 parallel Claims 27, 1, 24, 25, 28 and 29, respectively, but simply specify applying a thus effective amount of aspartylglucosaminidase (AGA).

The replacement language for the term "activator" has basis at least in paragraph **[0047]** of the originally filed specification and thus does not constitute new

matter. Of course, if the Examiner should prefer the original term "activator", applicants would be happy to amend the language to reinsert the original terminology.

The other amendments to the claims set forth above broaden the claims by allowing the possibility of aspartylglucosaminidase (AGA) being applied without the presence of the activator. While this possibility was not encompassed by the previous versions of the claims, it is not new matter because it is clearly encompassed by the original specification in numerous locations; see in particular, paragraphs **[0002]**, **[0018]**, **[0019]**, **[0020]***, **[0058]***, **[0065]**, **[0070]**, **[0071]**, **[0097]**, **[0098]**, **[00101]**, **[00102]**, **[00105]**, **[00106]**, Examples 1 and 2, and Example 3, Compositions 1, 2 and 3. Note most especially **[0020]** where the active ingredient is disclosed as being simply (i) and **[0058]**, where the composition comprising, (i) + (ii) is indicated as a preferred embodiment. It is also pointed out that the claim amendments are supported by the U.S. provisional application, the priority of which is claimed herein, said application being expressly incorporated by reference herein in paragraph **[0001]** of the as-filed specification. Provisional U.S. Application No. 60/441,741 was filed on January 23, 2003 in French. A verified English translation of the provisional application is being filed concurrently herewith in the provisional application file. A copy of the verified English translation of U.S. Provisional Application No. 60/441,741 is filed herewith for the Examiner's convenience. The provisional application's specification and claims likewise support the new claim language; see, in its English translation, page 1, lines 6-13; page 4, line 17 to page 5, line 9, especially page 5, lines 6-9, which indicates simply (i) as the active ingredient; page 13, lines 12-16; page 17, lines 14-19, which indicates (i) + (ii) as a

preferred embodiment; page 19, lines 11-16; page 21, line 11 to page 22, line 4; page 31, lines 8-18; page 32, line 20 to page 33, line 10; page 33, line 17 to page 34, line 24; Examples 1 and 2; Example 3, Compositions 1, 2 and 3; and the claims, especially Claims 18-23. Thus, the claims now in this application are well-supported by the application as originally filed.

SUMMARY OF SUBSTANCE OF TELEPHONE INTERVIEW

Applicants acknowledge and thank Examiner Fernandez for the courteous and constructive telephone interview with the undersigned on August 16, 2007.

In the telephone interview, applicants' representative indicated that an amendment was being prepared which would limit (i) to aspartylglucosaminidase (AGA) to address § 112, first paragraph, issues relating to the polypeptide. However, applicants' representative further indicate that it was discovered in the course of drafting amended claims that applicants' method claims did not cover an important embodiment of this invention, that is, the embodiment where only (i), now limited to aspartylglucosaminidase (AGA), is applied as the active ingredient, rather than both (i) and (ii) an activator. The present invention is indeed based on applicants' discovery that AGA is present in the epidermis in the *stratum corneum* and has a prodesquamating activity. See paragraph **[0016]** of the instant specification.

Applicants' representative asked the Examiner in the telephone interview if it would be possible at this stage of prosecution to amend the claims to include the possibility of requiring applying only (i) and making (ii) an optional additional ingredient, since the invention is based on the discovery of AGA in the *stratum corneum* and its prodesquamating activity therein, and both possibilities (i and i + ii)

are well within the original disclosure. The Examiner believed that her search of necessity would have already encompassed AGA alone and that, if the applicants showed that the original disclosure supported such claim amendments, she did not foresee a problem with examining claims amended in this manner. The foregoing amendment accordingly makes the proposed amendments and identifies the appropriate support in the as-filed application. The prior art rejection was not discussed in the telephone interview, nor were the § 112, first paragraph rejections relating to the "activator" ingredient. These will of course be addressed below.

ACKNOWLEDGMENT OF FOREIGN PRIORITY

Applicants thank the Examiner for acknowledging the claim for priority and the certified copy of the foreign priority document.

CLAIM REJECTIONS - 35 U.S.C. § 112

Claims 1, 9-11, 13, 14, 16, 17, 21, 24, 25, 27-29, 33 and 35-51 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants submit that all of their claims are free of this rejection.

With respect to the written description rejection based on the various polypeptides named in the claims, all of the claims are now limited to aspartylglucosaminidase (AGA), and the Examiner previously indicated that there was written description for aspartylglucosaminidase (AGA) in the June 26, 2006 Official Action, page 3, second paragraph. Thus, withdrawal of the written description rejection insofar as concerns the polypeptide is respectfully requested.

With respect to the written description requirement based on the activator, first of course, the claims now only encompass activators of aspartylglucosaminidase,

not of any of the other hydrolase polypeptides previously encompassed by the claim. Secondly, the specification does indeed provide appropriate written description for activators, that is, for compounds which stimulate the activity of AGA; not only does paragraph **[0050]** specifically exemplify sodium dodecyl sulfate and sodium lauryl ether sulfate, but also paragraphs **[0043]** through **[0048]**, which include various test methods, provide written description. It is certainly no more than routine experimentation to determine whether any given compound stimulates the activity of AGA. Applicants have described specific activators for AGA in paragraph **[0050]**, meeting the "particulars" required for sufficient description. There is no requirement to describe every compound that can activate AGA. Therefore, withdrawal of the written description requirement as to activators other than sodium dodecyl sulfate and sodium lauryl ether sulfate is respectfully requested. Moreover, while Claims 43-51 are free of this aspect of the written description requirement because they specify specifically disclosed activators, it is also pointed out that new Claims 61-66 are free of this aspect of the written description rejection because they do not require an activator.

Claims 43-60 have also been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Claims 52-60 have been cancelled as redundant as indicated hereinabove, but Claims 43-51 remain in the application. These appear to be the only claims now in the application to which this rejection would be applied, since new Claims 61-66 do not specify the presence of an activator. The specification clearly teaches that sodium dodecyl sulfate and sodium lauryl ether sulfate are activators of AGA; while admittedly no working examples are present in the specification, it is not believed that there is valid reason

to doubt the objective enablement provided by the specification. The Examiner believes that the Enomaa et al. publication provides reason to doubt the truth of the teaching in the specification. However, it is respectfully submitted that the Examiner has misinterpreted the Enomaa et al. article. The denaturing of AGA in the presence of SDS occurs only at elevated temperatures. Note the following discussion of Figs. 2 and 3 found on page 615 of Enomaa et al.

> If the AGA protein was not denatured by boiling with SDS before application on SDS/PAGE in Western-blot analysis, these antibodies identified a high-molecular-mass AGA band representing the native form of all the enzyme with detectable enzymatic activity (Fig. 2). Boiling of the enzyme with 0.5% SDS before SDS/PAGE and after Western-blot analysis resulted in the disappearance of the high-molecular-mass band and appearance of four bands of molecular mass 17/18kDa and 24/25dKa (Fig. 2). Further studies of the effect of SDS on the native AGA enzyme revealed that only temperatures higher than 60°C resulted in the decrease of AGA activity in the presence of 0.1-0.5% SDS at pH 7 (Fig. 3), demonstrating the AGA protein's exceptional resistance to SDS at lower temperatures. (Emphasis added.)

In accord with the above, Fig. 2, lanes 1, 3 and 5 show no breakdown of the AGA with 0.5% SDS. Lanes 2, 4 and 6, which were also heated at 100°C for 3 minutes, showed denaturing of the enzyme. In Fig. 3 and in Fig. 4, denaturing is not shown at lower temperatures. Therefore, the prior art does not teach anything contrary to the teachings of applicants' specification; therefore, because there is thus no reason to doubt the objective enablement provided by the specification, the specification must be accepted to be enabling and the enablement rejection should be withdrawn.

The enablement rejection is not applicable to new Claims 61-66, which do not require any activator.

CLAIM REJECTIONS - 35 U.S.C. § 103

Claims 1, 9-11, 13, 14, 16, 17, 21, 24, 25, 27-29, 33 and 35-42 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Fein US 2003/0026794 in view of Baumann et al., *Biochem. J.* 1989, 262:189-194. Applicants submit that all of the claims now in this application are patentable over Fein alone or in view of Baumann et al.

Applicants do not dispute that Fein discloses treatment of conditions which include those to which applicants' claims are directed. Indeed, Fein discloses treatment of a vast number of conditions involving various layers of skin, including deep dermal or subcutaneous layers, which are not encompasses by this invention. See, for example, paragraphs **[0029]** to **[0040]** of Fein describing numerous very different kinds of disorders. Further, Fein discloses many different enzymes in paragraph **[0044]** of his specification. Applicants can find little in Fein to lead one of ordinary skill to know which enzyme to use to treat which conditions, except in the case of trypsin or trypsin plus papain. With those exceptions, applicants submit that the Fein is not enabling. Furthermore, it is applicants who have discovered and shown in their application that aspartylglucosaminidase (AGA) is present in the epidermis in the *stratum corneum* and has a prodesquamating activity. It is this discovery which has led to the presently claimed methods. Fein does not even allude to the possibility of using aspartylglucosaminidase in his methods. AGA is not mentioned at all by Fein, much less the particular conditions of the numerous types disclosed therein which could be treated with AGA. There is certainly nothing in Fein

to lead one of ordinary skill to promoting desquamation of the skin by topically applying AGA. There was no reasonable expectation in the art that AGA would successfully promote desquamation when there is not even a reasonable exception that every specific enzyme mentioned by Fein would promote desquamation. It is clear that Fein worked only with trypsin and papain; he does not enable the thousands of specific enzyme and condition combinations his specification mentions, much less those he does not. He certainly does not mention aspartylglucosaminidase or AGA. Indeed, he worked only with two proteases, typsin and papain, which are very different from AGA. A person of ordinary skill in the art would recognize Fein's disclose as non-enabling, most particularly for the specific undisclosed enzyme AGA, because that skilled person knows that enzymes show very specific activity. In fact, two of the present inventors have described elsewhere, in published application US 2004/0015187 dated June 17, 2004 (a continuation of PCT/FR01/03551, which was published as WO 02/38122 A2 on May 16, 2002), that several enzymes from the same family (that is, able to break the same kind of bond) show different activity according to the tested substrate. See in particular Table 1 with different glycanases and Table 2 with different cellulases. This proves that different enzymes from the same family have different activity. US 2004/0115187 also shows that only some glycosidases (N-glycanase (endo F) show activity on *stratum corneum* desquamation whereas similar enzymes (exoglycosidases, especially O-glycanase) have no activity on desquamation. This shows that one cannot expect desquamating activity of an enzyme from the known activity of an enzyme from the same or a close family and directly contradicts the sweeping generalizations of the Fein document. Knowing this, one of ordinary skill would not

expect from the desquamating action shown by Fein for the proteolytic enzymes trypsin and papain or from the broad generalization of Fein, the desquamating action of AGA, an hydrolase with amidase activity which is a very different type of enzyme from trypsin and/or papain, which is not even mentioned by Fein and which applicants themselves have discovered is found in the *stratum corneum* and has a desquamating effect therein.

Baumann et al. disclose that aspartylglucosaminidase or AGA has been known to be present in a number of human tissues and body fluids and more specifically in hepatic tissues. A deficiency of AGA causes aspartylglycosaminuria (also called aspartylglucosaminuria), an autosomal recessive lysosomal storage disease. Baumann et al. characterize the polypeptide chains of AGA, but they do not remotely suggest that AGA is found in the *stratum corneum* and plays a desquamating role therein, therefore is uniquely well-suited for use in the desquamating methods claimed herein. No one prior to applicants found AGA in the *stratum corneum* or found it to have a desquamating action therein, which are the findings which led to the present invention. The combination of Baumann et al. with Fein does not cure the deficiencies in Fein and does not render the present invention obvious.

In view of the foregoing, it is submitted that the claims now in this application are patentable over Fein alone and over Fein in view of Baumann et al.

As to the Examiner's assumption that a buffer at a pH of about 6 is one of applicants' activators, it is respectfully submitted that applicants separately acknowledge the important of pH in paragraph **[0085]**; therefore, it is believed to be taking applicants' "activator" out of context to hold that a buffer is an activator. At

any rate, this does not succeed in overcoming the basic deficiencies of Fein or Fein in view of Baumann et al. and cannot render the subject matter of any of the claims which require an activator to be obvious. And it of course is not relevant to the claims herein which do not require the presence of an activator.

PREVIOUS 35 U.S.C. §§ 102 AND 103 REJECTIONS

Applicants acknowledge and thank the Examiner for withdrawing the previous rejections over Meyers, Rudolph-Owen et al., Van de Sandt et al. and Martinez in light of applicants' arguments.

CONCLUSION

In light of the foregoing, it is believed that all of the claims now in this application are in allowable form. Further, favorable action in the form of a Notice of Allowance are believed to be next in order and are earnestly solicited.

Respectfully submitted,

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